

### **REMARKS / ARGUMENTS**

The specification is amended to remove an embedded hyperlink. No new matter is added by this amendment.

Claims 69-72, 75, 77, 78, 81-106 are currently pending in the application. Claim 69 has been amended. No new matter has been added by way of this amendment, and support can be found in the specification, *e.g.*, in the Examples. Claims 77, 92-101 and 104-106 are canceled herein without prejudice to Applicants' right to pursue the subject matter of these claim in a related application. Upon entry of the present Amendment, claims 69-72, 75, 78, 81-91, 102 and 103 will be pending.

#### **The Objection to the Specification**

The Examiner has objected to the specification as including an embedded hyperlink at page 22, and has suggested deleting "http://". Applicants have deleted "http://" in the paragraph bridging pages 21 and 22. Applicants respectfully request that the Examiner withdraw the objection to the specification.

#### **I. Rejections Under 35 U.S.C. § 112, First Paragraph**

The Examiner has made a number of rejections under 35 U.S.C. § 112, first paragraph regarding alleged lack of written description. Applicants address each of these rejections separately below.

##### **A. Claims 69-72, 75, 77, and 88-91 (New Matter)**

The Examiner has rejected claims 69-72, 75, 77, and 88-91 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification. Specifically, the Examiner contends that there is no disclosure of a Smurf having the activity of a Smurf with greater than 80% identity to SEQ ID NO:2. (Office Action, page 3). Without conceding the correctness of the Examiner's basis for rejection, and solely to further prosecution of the claims, Applicants have amended claim 69 to specify that the Smurf activity detected is the activity of a Smurf comprising greater than 90% identity with the amino acid sequence of SEQ ID NO:2. Support for this amendment is found at least on page 21 of the specification as filed. As such, this amendment adds no new matter. Applicants respectfully request that the Examiner withdraw this rejection of the claims.

**B. Claims 69-72, 75, 77, and 81-91 (Written Description)**

The Examiner has rejected claims 69-72, 75, 77, and 81-91 under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient written description (Office Action, pages 4-10). Specifically, the Examiner contends that the claims do not recite any functional limitations, and that there is an inadequate description of the genus recited in the claims, *i.e.*, a Smurf having an amino acid sequence similarity of greater than 80% to SEQ ID NO:2.

Without conceding the propriety of the Examiner's rejections, and solely to further prosecution of the claims, Applicants have amended claim 69 to specify that the Smurf activity detected is the activity of a Smurf comprising greater than 90% identity with the amino acid sequence of SEQ ID NO:2, and to specify that the Smurf activity detected is ubiquitination of a Smad polypeptide in a host cell, ubiquitination of a TGF $\beta$  receptor, or interaction of a Smurf WW domain with a PPXY domain of a Smad polypeptide. Thus, the genus of polypeptides encompassed by the claims comprises a relatively small number of variants of the specifically-disclosed SEQ ID NO:2, and these variants each have a function specified by the claims.

In this respect, the claims as amended correspond to the Revised Interim Written Description Guidelines Training Materials, which state that a claim to a protein having a given SEQ ID NO and variants thereof having a sequence similarity of 95% and that catalyze a reaction  $A \rightarrow B$  comply with the written description requirement. In this Training Materials example, the specification discloses the sequence, and the procedures for making variants of the sequence are "conventional in the art." The single species disclosed in the Training Materials example is deemed representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of the sequence which are capable of the specified catalytic activity.

In like fashion, the small number of variants encompassed by claim 69 as amended recites each share at least 90% structural similarity to SEQ ID NO:2, and are identifiable as having at least one specifically-recited function. The specification provides extensive guidance at pages 24-27 as to how to obtain Smurf variants (*e.g.*, insertions, deletions, substitutions, *etc.*), using techniques "conventional in the art" at the time the application was filed (*see, e.g.*, Sambrook *et al.*, 1989, cited on page 26, line 29 of the specification), and

assays of Smurf activity (*see, e.g.*, pages 45-67). Thus, claim 69, and the claims depending therefrom, conform to the Written Description Guidelines.

Applicants additionally point out that claim 75 encompasses the use of an even smaller set of polypeptides, as each of the recited polypeptides must have the activity of a Smurf *comprising* the amino acid sequence of SEQ ID NO:2. This Smurf is very well-described in the specification, for example at FIG. 10, SEQ ID NO:2, and in Example 1.

The Examiner contends that the specification does not identify conserved regions of SEQ ID NO:2. Office Action at page 9. However, the application provides specific information about functional domains and conserved regions of SEQ ID NO:2. For example, the specification identifies regions of SEQ ID NO:2 that comprise the WW and HECT domains. *See, e.g.*, FIG 1 and accompanying text at page 5, identifying the two WW protein interaction domains and the HECT domain); FIG. 13 (diagramming the domains of Smurf1). Moreover, the specification identifies regions of SEQ ID NO:2 that are conserved with respect to other Smurf proteins. *See, e.g.*, FIG. 1, showing sequence identities between human Smurf 1 (SEQ ID NO:2), *Xenopus laevis* Smurf 1, and *Saccharomyces pombe* pub 1 (a ubiquitin ligase). Given this information, in view of the functional limitations of the polypeptides encompassed by the claims, a person of skill in the art would be able to easily envisage regions of SEQ ID NO:2 to modify to preserve function. Moreover, FIG. 1 demonstrates that there are numerous sites, even within the functional regions of SEQ ID NO:2, that could be varied with a reasonable expectation of retaining function. Variants of SEQ ID NO:2 that have at least 90% similarity to SEQ ID NO:2 are, therefore, fully described in the specification.

Thus, claim 69 as amended recites a relatively small genus of polypeptides, based on SEQ ID NO:2, the structure, conserved regions and functional domains of which are well-described in the specification, and specifies two functions the recited Smurf must have in the assay. As such, claim 69, and claims depending from claim 69, have sufficient written description support in the specification. For the reasons stated above, Applicants respectfully request that the Examiner withdraw this rejection of the claims.

### **C. Claims 92-106**

The Examiner has rejected claims 92-106 under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient written description. Office Action at page 10. Specifically, the

Examiner contends that, without recitation of a structural limitation, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides.

Without conceding the propriety of the Examiner's rejections, and solely to further prosecution of the remaining claims, Applicants have herein canceled claims 92-101 and 104-106. Applicants request that the Examiner withdraw this rejection with respect to these claims.

Claims 102 and 103 have not been canceled because these claims depend from claims 69 and 78, respectively. As explained in this paper, claims 69 and 78, as amended are sufficiently described by the specification. Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 102 and 103 on this basis.

**D. Claims 78, 86, 87**

The Examiner has rejected claims 78, 86 and 87 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed (Office Action, pages 14-15). Specifically, the Examiner contends that the claims do not specify what Smurf activity is being monitored

Without conceding the propriety of the Examiner's rejections, and solely to further prosecution of the claims, Applicants have amended claim 78 to recite that the Smurf activity is ubiquitination of a Smad polypeptide in a host cell, interaction of a Smurf WW domain with a PPXY domain of a Smad polypeptide, or ubiquitination of a TGF $\beta$  receptor. Thus, claim 78 as amended, and the claims depending from claim 78, specify the function being monitored.

The Examiner further appears to contend that the claims do not specify what Smurf activity is being monitored because Smurf 1, Smurf 2, and Dsmurf have different activities. Office Action at page 14. To this end, the Examiner states that, though Applicant has argued that SEQ ID NO:4 is human Smurf2, "Applicant is arguing a limitation not evidenced by the present claim language." Office Action at page 15. However, SEQ ID NO:4 is *defined* by the specification to be a human Smurf2 (*see, e.g.*, page 4, line 18). The fact that SEQ ID NO:4 is a human Smurf2 is inherent in the sequence; the sequences of hSmurf1 and Dsmurf are different. However, solely in an effort to further prosecution of the claims, Applicant has amended claim 78 to specify that the Smurf activity, the modulation of which is detected, is

that of a *human* Smurf. As such, claim 78, and claims 86 and 87, which depend from claim 78, are sufficiently described in the specification.

Thus, for at least these reasons, Applicants respectfully request that this rejection of the claims be withdrawn.

**II. Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)**

The Examiner has rejected claims 69-72, 75, 77, 88-91 and 102 under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. Office Action at page 15. As a basis for this rejection, the Examiner reiterates the bases on which these claims were rejected for alleged lack of written description. Applicants acknowledge that the Examiner has deemed the claims to be enabled at least with respect to SEQ ID NO:2. Applicants also acknowledge that the Examiner has deemed these claims to be enabled for SEQ ID NO:4; however, none of the claims rejected on this basis recites SEQ ID NO:4. Applicants will proceed on the assumption that the rejection is directed only to SEQ ID NO:2. As noted above, claim 77 is canceled herein without prejudice.

MPEP § 2164.01 states that 35 U.S.C. § 112, first paragraph, “has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation.” The same section further states that “[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.”

The genus of polypeptides recited in claim 69 is far smaller than the “infinite number of fragments” the Examiner contends the claim specifies. For example, claim 69, as amended, requires that the recited Smurf not only share at least 90% sequence similarity to SEQ ID NO:2, but comprise both a WW domain and a HECT domain. The boundaries of these domains are clearly described in FIGS. 1 and 13. Moreover, claim 69, as amended, specifies that the Smurf activity is either ubiquitination of a Smad 1 polypeptide or interaction of a Smurf WW domain with a Smad PPXY domain.

Given this description of the recited Smurfs, one of ordinary skill in the art would be able to identify and utilize such Smurf polypeptides for use in the methods of the invention without undue experimentation. For example, the specification provides extensive guidance as to how to clone Smurf family genes (*e.g.*, at pages 23-24) and express Smurf family proteins (*e.g.*, at pages 27-39). The Examiner is also directed to Example 1, wherein human, mouse and *Xenopus* Smurf1 were identified. Additionally, the specification provides

extensive guidance at pages 24-27 as to how to obtain Smurf derivatives (*e.g.*, insertions, deletions, substitutions, *etc.*) using techniques well-known to skilled artisans at the time the application was filed (*see, e.g.*, Sambrook *et al.*, 1989, cited on page 26, line 29 of the specification). Additionally, Applicants have provided extensive guidance as to how to create mutants and derivatives of Smurf. (*see, e.g.*, page 24, line 15 - page 27, line 10). Any experimentation involved in identifying and producing Smurf proteins suitable for use in the claimed method is therefore routine and not undue.

Even if some of the species in a genus claim are inoperative, the claims are not necessarily invalid. *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1576; 224 U.S.P.Q. (BNA) 409. “It is not a function of the claims to specifically exclude...possible inoperative substances....” *Id.* (*citing In re Dinh-Nguyen*, 492 F.2d 856, 858-59, 181 U.S.P.Q. (BNA) 46, 48 (CCPA 1974) (emphasis omitted); *accord, In re Geerdes*, 491 F.2d 1260, 1265, 180 U.S.P.Q. (BNA) 789, 793 (CCPA 1974); *In re Anderson*, 471 F.2d 1237, 1242, 176 U.S.P.Q. (BNA) 331, 334-35 (CCPA 1973)).

The Examiner cites Seffernick *et al.*, *J. Bacteriol.* 183:2405-2410 (2001) (“Seffernick”) in support of the contention that changes in polypeptide sequences are unpredictable. Office action at page 18. This paper is not relevant to the present rejection for two reasons. First, the paper does not disclose Smurfs. As such, this paper provides no information on the sensitivity, or lack thereof, of Smurfs to changes in amino acid sequence. Second, it is clear that the fact that the two proteins disclosed in Seffernick, which possessed different functions while sharing most of their respective sequences, was highly unusual. As such, Seffernick is not a model of the effects on sequence variations on protein activity that is generally applicable, let alone applicable to Smurfs.

The Examiner further opines that “[m]aking and testing the infinite number of possible variants to find one that functions as described is undue experimentation” (Office Action, page 20). The number of variants encompassed by the claims is not “infinite.” Moreover, it was routine at the time the application was filed to screen large amounts of mutants, for example in high-throughput screening assays, for functional activity. Indeed, Guo (*Proc. Nat’l Acad. Sci. U.S.A.* 101(25):9205-9210 (2004) demonstrates that it is quite straightforward, starting from a particular sequence, to generate mutants and determine functionality. *See, e.g.*, MPEP § 2164.01 (“[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.”).

In addition, as explained above, claim 75 specifies that the Smurf activity detected is the activity of a Smurf comprising SEQ ID NO:2. This Smurf is very well-described in, and enabled by, the specification, for example at FIG. 10, SEQ ID NO:2, and in Example 1. Thus, claim 75 is clearly enabled.

Thus, Applicants submit that claims 69-72, 75, 88-91 and 102 are fully enabled and comply with all the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

### **III. Conclusion**

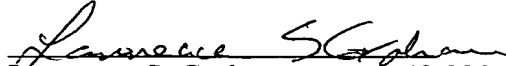
In view of the foregoing remarks, Applicants respectfully submit that this application is now in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

A Petition for a one (1) month Extension of Time under 37 C.F.R. § 1.136(a) is filed concurrently herewith (in duplicate), which extends the response period from December 27, 2005 to and including January 27, 2006. The Petition further authorizes the PTO to charge the one month extension fee of \$120 to our Deposit Account No. 50-3013. No additional fees are believed due in connection with this Amendment. However, if there are any other fees due, please charge them to Deposit Account 50-3013. If a request for extension of time and fee are required under 37 C.F.R. § 1.136 that have not been accounted for, such an extension

is requested and the fee should be charged to our Deposit Account. Also, please charge any fees underpaid or credit any fees overpaid to the same Deposit Account.

Respectfully submitted,

Date: October 17, 2006

  
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